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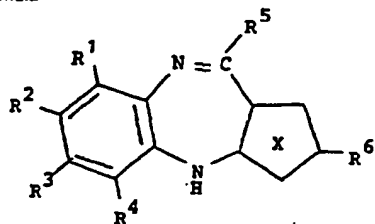
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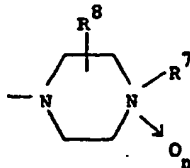
Claims for the following Contracting States: ES + GR.

⑳ Benzodiazepine compounds and their use as pharmaceuticals.

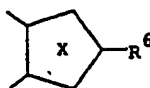
㉑ Pharmaceutical thiazolo-[1,5]benzodiazepines of the formula



in which R¹, R², R³ and R⁴ are independently hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, halogen, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkylthio or phenylsulphonyl; in which R⁵ is a group of the formula formula



where R⁷ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, benzyl or ZO-C₂₋₆ alkyl where Z is hydrogen or an acyl group, R⁸ is hydrogen or C₁₋₄ alkyl and n is 0 or 1, provided that when R⁷ is hydrogen n is 0; in which R⁶ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy or C₁₋₄ alkylthio; and in which



represents a thiazole ring selected from



and acid addition salts thereof.

The compounds have central nervous system activity.

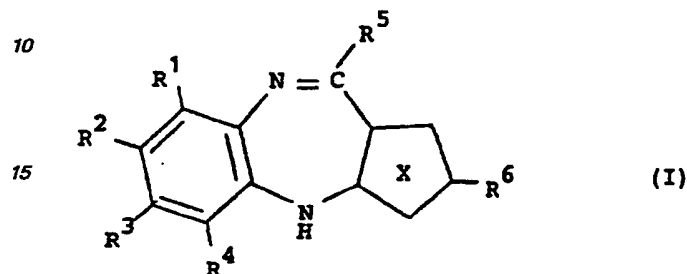
Description

BENZODIAZEPINE COMPOUNDS AND THEIR USE AS PHARMACEUTICALS

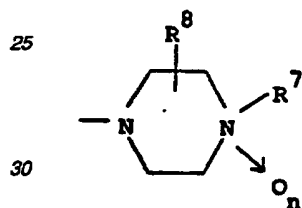
This invention relates to novel compounds, processes for preparing them and their use as pharmaceuticals.

Various tricyclic compounds with pharmaceutical properties have already been investigated, and for example British Patent 1 533 235 discloses some thieno-benzodiazepine compounds of this type. Such compounds are described as having useful activity on the central nervous system.

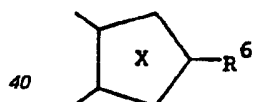
The compounds of the invention are thiazolo-[1,5]benzodiazepines of the following formula



20 in which R¹, R², R³ and R⁴ are independently hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, halogen, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkylthio or phenylsulphonyl; in which R⁵ is a group of the formula



35 where R⁷ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₄ alkyl, benzyl or ZO-C₂₋₆ alkyl where Z is hydrogen or an acyl group, R⁸ is hydrogen or C₁₋₄ alkyl and n is 0 or 1, provided that when R⁷ is hydrogen n is 0; in which R⁶ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy or C₁₋₄ alkylthio; and in which



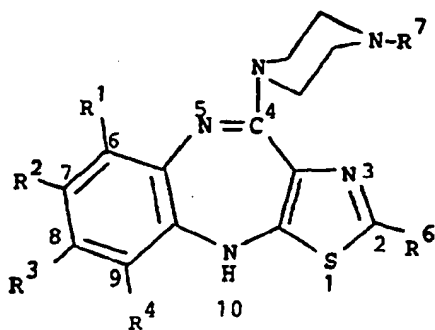
represents a thiazole ring selected from



50 and acid addition salts thereof.

Compounds of formula (I) have been found to possess useful biological properties and the invention includes a compound of formula (I) for use as a pharmaceutical, especially for use in treating disorders of the central nervous system.

55 A preferred group of compounds of formula (I) is one in which R¹, R², R³ and R⁴ independently represent hydrogen, halogen or C₁₋₄ haloalkyl, R⁶ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl or C₁₋₄ alkylthio, R⁷ is hydrogen or C₁₋₄ alkyl, R⁸ is hydrogen and n is 0, being of the formula:

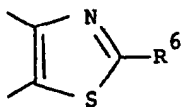


and acid addition salts thereof.

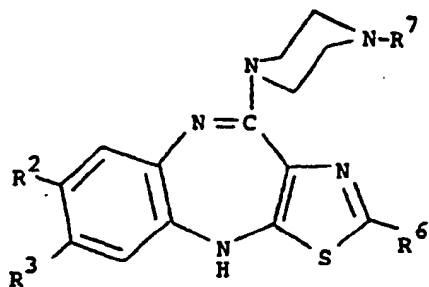
In the above general formula (I), the term "C₁₋₁₀ alkyl" means a straight or branched chain alkyl group containing 1 to 10 carbon atoms and is especially "C₁₋₆ alkyl", for example, methyl, ethyl, isopropyl, propyl, butyl, sec. butyl, isobutyl, tert. butyl, pentyl or hexyl. A preferred alkyl group is "C₁₋₄ alkyl". The term "C₁₋₄ haloalkyl" means any such alkyl group substituted by one or more, preferably three halogen atoms, and is especially trifluoromethyl. The term "halogen" is preferably bromine, fluorine and chlorine, and especially chlorine and fluorine. The terms "C₁₋₄ alkoxy" and "C₁₋₄ alkylthio" mean any C₁₋₄ alkyl group attached through an oxygen or sulphur atom to a ring atom and "C₁₋₄ haloalkoxy" means a C₁₋₄ alkoxy group substituted by one or more, preferably three halogen atoms and is especially trifluoromethoxy. The term "C₂₋₄ alkenyl" refers to groups such as vinyl, allyl and butenyl. "C₃₋₇ Cycloalkyl" means a saturated ring having 3 to 7 carbon atoms in the ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, which can, in the group "C₃₋₇ cycloalkyl C₁₋₄ alkyl", be attached to the ring via an alkyl chain having 1 to 4 carbon atoms.

When R⁷ is ZO-C₂₋₆ alkyl, Z is hydrogen or an acyl group. Preferably when Z is an acyl group, the group is of the formula RCO- where R is C₁₋₂₀ alkyl, for example, C₁₀₋₁₂ alkyl. Preferred examples of R⁷ of this type are hydroxyethyl or hydroxypropyl of the formula -(CH₂)_mOH where m is 2 or 3.

The R⁶ and R⁷ groups are preferably C₁₋₄ alkyl, for example methyl or ethyl. Preferably also R¹, R⁴ and R⁸ are hydrogen, and n is 0, and X is



A particular group of compounds is one of the following formula



in which R² and R³ independently represent hydrogen or halogen, R⁶ is C₁₋₄ alkyl and R⁷ is C₁₋₄ alkyl.

Examples of the compounds of the invention are as follows:

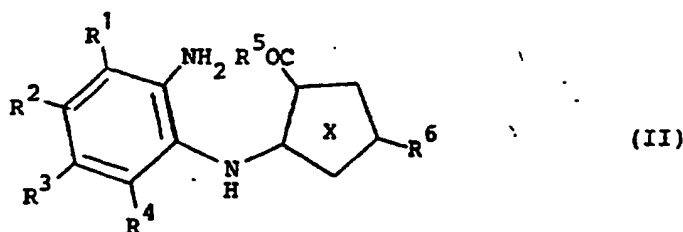
- 8-Fluoro-2-methyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5]benzodiazepine
- 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5]benzodiazepine
- 7-Fluoro-2-methyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5]-benzodiazepine
- 7-Chloro-2-methyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5]-benzodiazepine
- 7,8-Difluoro-2-methyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5]-benzodiazepine
- 2-Ethyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5]benzodiazepine
- 2-Ethyl-8-fluoro-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5]benzodiazepine
- 2-Ethyl-7-fluoro-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5]benzodiazepine
- 7-Chloro-2-ethyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5]benzodiazepine
- 4-(8-Fluoro-2-methyl-10H-thiazolo[5,4-b][1,5]benzodiazepin-4-yl)-1-methyl piperazine-1-oxide
- 4-(2-Methyl-10H-thiazolo[5,4-b][1,5]benzodiazepin-4-yl)-1-methyl piperazine-1-oxide

4-(7-Fluoro-2-methyl-10H-thiazolo[5,4-b][1,5]benzodiazepin-4-yl)-1-methyl piperazine-1-oxide
 4-(7-Fluoro-2-methyl-10H-thiazolo[5,4-b][1,5]benzodiazepin-4-yl)-piperazine-1-ethanol
 4-(7-Chloro-2-methyl-10H-thiazolo[5,4-b][1,5]benzodiazepin-4-yl)-1-methyl piperazine-1-oxide
 8-Fluoro-2-methyl-10-(4-methyl-1-piperazinyl)-4H-thiazolo[4,5-b][1,5]benzodiazepine
 2-Methyl-10-(4-methyl-1-piperazinyl)-4H-thiazolo[4,5-b][1,5]benzodiazepine
 7-Fluoro-2-methyl-10-(4-methyl-1-piperazinyl)-4H-thiazolo[4,5-b][1,5]benzodiazepine
 7-Chloro-2-methyl-10-(4-methyl-1-piperazinyl)-4H-thiazolo[4,5-b][1,5]benzodiazepine;
 and acid addition salts thereof.

As indicated above, the compounds of the invention are useful both in their free base and acid addition salt forms. The acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric or lactic acid, or organic sulphonic acids for example methane sulphonic, ethane sulphonic, 2-hydroxyethane sulphonic, toluene-p-sulphonic or naphthalene-2-sulphonic acid. Apart from pharmaceutically acceptable acid addition salts, other salts are also included within the scope of acid addition salts such as, for example, those with picric or oxalic acid, since they may serve as intermediates in the purification of the compounds or in the preparation of other, for example, pharmaceutically acceptable, acid addition salts, or are useful for identification, characterization or purification of the bases.

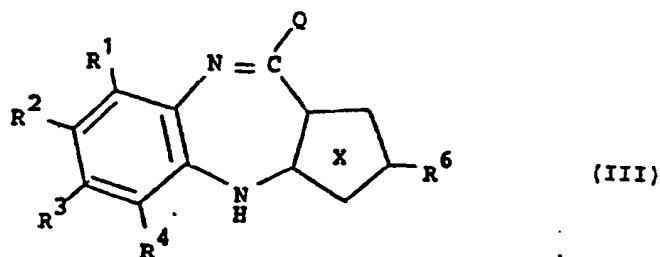
According to a further aspect of the invention there is provided a process for producing a compound of formula (I) or an acid addition salt thereof, which comprises

(a) ring-closing a compound of formula (II)



in which R¹ to R⁶ and X have the values defined above, optionally followed when R⁷ is hydrogen by alkylation to give a compound in which R⁷ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, benzyl or ZO-C₂₋₆ alkyl where Z is hydrogen or an acyl group,

(b) reacting an amine of formula R⁵H with a compound of formula (III)



in which R¹ to R⁶ and X have the values defined above and Q represents a radical capable of being split off with the hydrogen atom of the amine R⁵H, optionally followed when R⁷ is hydrogen by alkylation to give a compound in which R⁷ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, benzyl or ZO-C₂₋₆ alkyl where Z is hydrogen or an acyl group, or

(c) oxidising a compound of formula (I) in which R⁷ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, benzyl or ZO-C₂₋₆ alkyl where Z is an acyl group and n is 0, to give a compound in which n is 1.

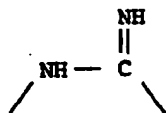
The above processes are of a general type previously described in the literature and appropriate reaction conditions, and suitable Q radicals can be readily chosen.

In reaction (a), compounds of formula (II) may be ring-closed by employing, for example, as catalyst titanium tetrachloride and as solvent anisole, and preferably at a temperature of 100°C to 250°C, for example from 150°C to 200°C. The compounds of formula (II) are preferably prepared *in situ* without isolation, as described below.

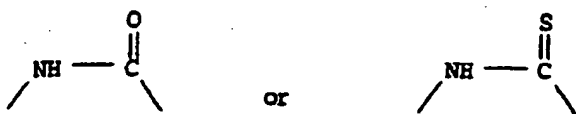
It may be mentioned, for example, that in reaction (b) the radical Q can be an amino group or a mono- or dialkyl-substituted amino group (each alkyl substituent containing 1 to 4 carbon atoms), hydroxyl, thiol, or an alkoxy, alkylthio or alkylsulphonyl group containing 1 to 4 carbon atoms, for example a methoxy or methylthio

group, or a halogen atom, especially a chlorine atom. Preferably, Q is amino (NH₂), hydroxyl or thiol, and amino is most preferred. The reaction is preferably carried out at a temperature of from 50°C to 200°C.

When Q is amino the intermediates of formula (III) may also exist in the imino form:



and when Q is hydroxyl or thiol, the intermediates of formula (III) may exist in their amide and thioamide forms:



The amidines of formula (III) (Q is NH₂), can be in a salt form for example as the hydrochloride, and they can be reacted with amines of formula R⁵H, optionally diluted with a solvent such as anisole, toluene, dimethylformamide or dimethylsulphoxide, and at a temperature range of 100 to 150°C. Alternatively the amine can be converted into the corresponding amide of formula (III) (Q is OH) by alkaline hydrolysis.

When Q is hydroxyl, reaction (b) can be accomplished in the presence of titanium tetrachloride which has the ability to react with the amine of formula R⁵H to form a metal amine complex. Other metal chlorides such as those of zirconium, hafnium or vanadium may also be employed. The reaction can be carried out in the presence of an acid binding agent such as a tertiary amine, for example, triethylamine.

Alternatively, the reaction can be carried out using excess of the amine of formula R⁵H to act as an acid-binding agent. A suitable organic solvent such as toluene or chlorobenzene can be used as a reaction medium, although it has been found that the use of anisole is particularly desirable, at least as a co-solvent, in view of its ability to form a soluble complex with TiCl₄.

If desired, elevated temperatures, for example up to 200°C, can be used to expedite the reaction and a preferred temperature range for carrying out the reaction is from 80°C to 120°C.

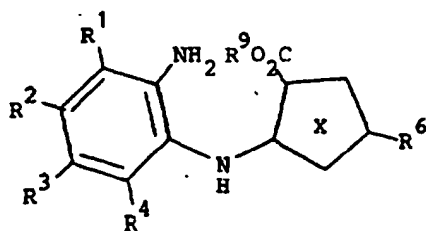
Thioamides of formula (III) (Q is SH), iminothioethers, iminoethers or iminohalides, or other derivatives containing active Q radicals as specified above, tend to be more reactive towards the amine R⁵H and can usually be reacted without the necessity for the presence of TiCl₄, but otherwise employing the same conditions of temperature and solvent.

When it is desired to prepare a compound in which R⁷ is other than hydrogen, it is preferred to start with the reactants of formula (II) or amine of formula R⁵H, in which R⁷ has the required value, and then to perform reaction (a) or (b). However, as an alternative, the corresponding compound of formula (I) in which R⁷ is hydrogen may first be prepared and this then reacted with a suitable alkylating agent of formula R⁷X by conventional methods employing an inert solvent and base, X being a leaving group such as for example chlorine, bromine or iodine, or a group such as tosyl or mesyl.

As mentioned above, in reaction (c), compounds of formula (I) in which R⁷ is other than hydrogen and n is 1, can be made by oxidation of the corresponding compounds in which n is 0. Suitable oxidising agents include for example m-chloroperbenzoic acid and the reaction is preferably carried out in an inert solvent such as for example dichloromethane, at a temperature of from -20°C to +20°C for example from -10°C to +10°C.

The compounds of formula (I) produced by the above processes may be isolated per se or may be converted to their corresponding acid addition salts using conventional methods.

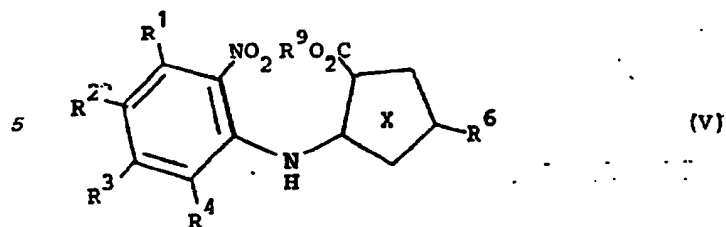
Intermediate compounds of formula (II) in process (a) described above, are preferably prepared in situ without isolation by reacting a compound of formula



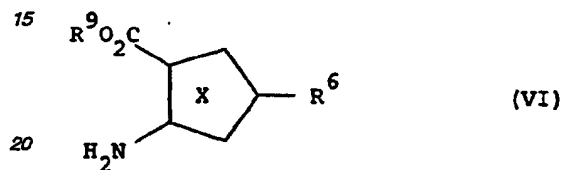
(IV)

in which R¹ to R⁴ and R⁶ have the values defined above and R⁹ is an ester group, preferably C₁₋₄ alkyl, with an amine of formula R⁵H, such as by heating to a temperature between 30°C and 120°C, for example about 100°C, in a suitable solvent such as for example anisole, and employing TiCl₄ as catalyst.

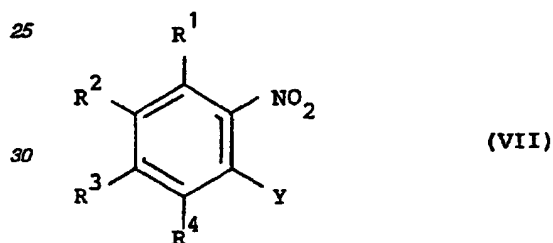
Compounds of formula (IV) can be prepared from the corresponding nitro compounds of formula



10 , if convenient, without isolation, for directly reacting with amine R^5H . Intermediate compounds of formula (V) are novel and are included as an aspect of the present invention. They can be made by condensation of a thiazole compound of formula



with an ortho-halonitrobenzene of formula



35 where Y is a halogen, preferably fluorine, bromine or chlorine, in the presence of a base, for example, sodium hydride, in a solvent such as for example tetrahydrofuran and at a temperature of from -20°C to 30°C , or anhydrous potassium carbonate in a solvent such as dimethylsulphoxide at a temperature of from 90°C to 120°C . Compounds of formula (V) are converted to the compounds of formula (IV) by reduction, for example catalytically, employing for instance, hydrogen and palladium/carbon or chemically, employing for example, stannous chloride and hydrogen chloride in aqueous ethanol, or ammonium polysulphide.

40 An illustration of the preparation of representative compounds of the invention (4-(4-alkyl-1-piperazinyl)-10H-thiazolo[5,4-b][1,5] benzodiazepines) by this route is given in the reaction scheme below:

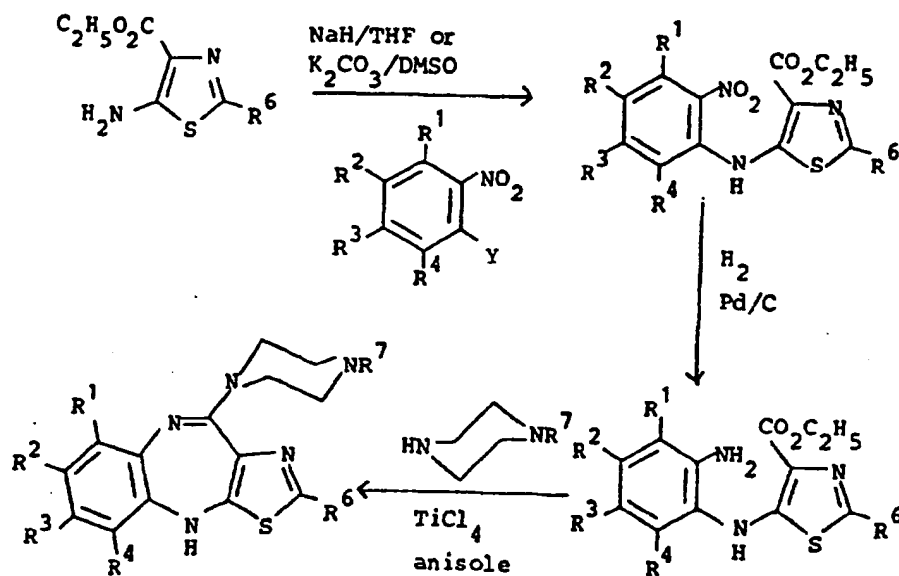
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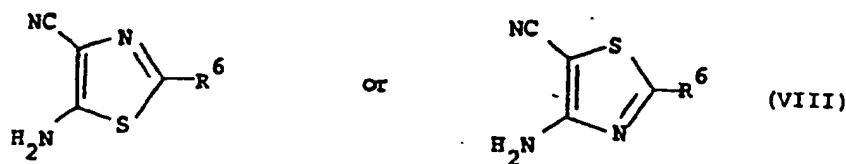
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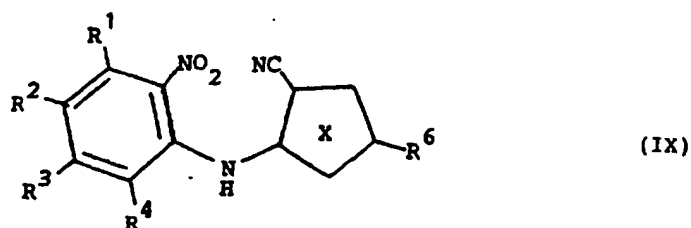
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The intermediate amidines of formula (III) (Q is NH₂), employed in process (b), can be prepared by condensation of a thiazole of formula



with an ortho-halonitrobenzene of formula (VII) above, in the presence of a base for example, sodium hydride in a solvent such as tetrahydrofuran or *n*-butyl lithium in tetrahydrofuran, or potassium carbonate in dimethylsulphoxide or with a tetraalkylammonium salt in a two-phase system, to form a nitronitrile of formula:



which can be simultaneously reduced and ring-closed to the amidine of formula (III) employing for example, stannous chloride and hydrogen chloride in aqueous ethanol or, alternatively by reduction with hydrogen and palladium/carbon or ammonium polysulphide followed by acid-catalysed ring closure.

Similarly, the intermediates amides of formula (III) (Q is OH), employed in process (b), can be derived from compounds of formula (IV) above, by ring closure employing for example sodium methylsulphonyl methanide in a suitable solvent such as dimethylsulphoxide can give an amide of formula (III) (Q is OH). Alternatively, these amides can be prepared by ring closure of an amino-acid, employing for example dicyclohexylcarbodiimide (DCC) in a suitable solvent such as tetrahydrofuran. These amino-acids can be obtained for example from the esters of formula (IV) by basic hydrolysis using for example sodium hydroxide in ethanol.

Thioamides of formula (III) (Q is SH) can be prepared by treating a solution of the corresponding amide in an anhydrous basic solvent such as for example pyridine with phosphorus pentasulphide. Similarly, the amides can be converted to iminothio ethers, iminoethers or iminohalides, or other derivatives containing active Q radicals, by treatment with conventional reagents such as for example in the case of an iminochloride, phosphorus pentachloride.

Thiazole starting materials of formulae (VI) and (IX), used in the processes described above, are either

known compounds, see for example Chem. & Ind. (1970) 1470; J.Chem.Soc. (1947) 1594, 1598; (1948) 2028; (1959) 4040; J.Prakt.Chem. (1967) 35 70; Arch.Pharm. (Weinheim) (1970) 303 625; Tetrahedron Lett. (1981) 22 2285; Monatsch.Chem. (1981) 112 1393; Bull.Chem.Soc. Japan (1983) 56 3851; J.Prakt. Chem. (1985) 327 604; Liebigs Ann.Chem. (1986) 780; or can be prepared by conventional techniques from known compounds. The

5 ortho-halonitrobenzene intermediates are either commercially available or can be simply prepared from commercially available substances.

As mentioned above, the compounds of the invention have useful central nervous system activity. This activity has been demonstrated in animal models using well-established procedures. In behavioural studies in mice, for instance, the compounds of the invention described in the following Examples were observed to

10 produce activity decrease at a dose range of 1.6 to 200 mg/kg p.o. In addition compounds have been found to be active in the spiroperidol binding test described by P. Seeman et al., in Nature 261, 717-719 (1976) and for example have an IC₅₀ value (the concentration of the compound required to reduce the binding of spiroperidol by 50 per cent) of less than 1 µM. Thus the compounds are potent centrally acting agents with neuroleptic, sedative or relaxant, anxiolytic or anti-emetic properties. These properties, coupled with their high therapeutic

15 index, render them useful in the treatment of certain kinds of psychotic conditions such as schizophrenia and acute mania and of mild anxiety states.

The compounds of this invention are effective over a wide dosage range, the actual dose administered being dependent on such factors as the particular compound being used, the condition being treated and the type and size of mammal being treated. However, the dosage required will normally fall within the range of 0.01 to 2

20 mg/kg per day, for example in the treatment of adult humans, dosages of from 0.5 to 100 mg per day may be used.

The compounds of the invention will normally be administered orally or by injection and, for this purpose, the compounds will normally be utilised in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

25 Accordingly the invention includes a pharmaceutical composition comprising as active ingredient a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable carrier. In making the compositions of the invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or

30 liquid material which acts as a vehicle, excipient or medium for the active ingredient. Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoate, talc, magnesium stearate or mineral oil. The compositions of the invention may, if desired, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

35 Depending on the route of administration, the foregoing compositions may be formulated as tablets, capsules or suspensions for oral use and injection solutions for parenteral use or as suppositories. A preferred formulation is an injection especially a sustained release formulation for intra-muscular injection. Preferably the compositions are formulated in a dosage unit form, each dosage containing from 0.5 to 100 mg, more usually 1 to 100 mg, of the active ingredient.

40 The following Examples illustrate the invention:

EXAMPLE 1

Ethyl 5-(5-fluoro-2-nitrophenylamino)-2-methylthiazole-4-carboxylate

45 Ethyl 5-amino-2-methylthiazole-4-carboxylate (Chem. & Ind. (1970) 1470) (3.72 g) 2,4-difluoronitrobenzene (3.2 g) and potassium carbonate (5.6 g) were stirred under a nitrogen atmosphere in dimethylsulphoxide (80 ml) at 110°C for 50 minutes. The mixture was poured onto a mixture of crushed ice and 2M hydrochloric acid (100 ml) and extracted into dichloromethane. The extract was washed with water, dried with magnesium sulphate and the solvent removed to leave the product, which was purified by chromatography on a column of

50 silica and recrystallisation from ethanol, m.p. 179-182°C.

Similarly prepared were:-

Ethyl 5-(4-fluoro-2-nitrophenylamino)-2-methylthiazole-4-carboxylate, m.p. 170-174°C

Ethyl 5-(4-chloro-2-nitrophenylamino)-2-methylthiazole-4-carboxylate, m.p. 175-181°C

Ethyl 5-(2-nitrophenylamino)-2-methylthiazole-4-carboxylate, m.p. 133-134°C.

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EXAMPLE 2

Ethyl 5-(2-nitrophenylamino)-2-methylthiazole-4-carboxylate

60 To sodium hydride (50% oil dispersion, 1.44 g) in dry tetrahydrofuran (25 ml) under a nitrogen atmosphere was added ethyl 5-amino-2-methylthiazole-4-carboxylate (2.78 g) and o-fluoronitrobenzene (2.82 g) in tetrahydrofuran (100 ml). The mixture was stirred at 25°C for 20 hours and carefully poured onto excess crushed ice. The mixture was acidified with 2M hydrochloric acid and the precipitate filtered, washed with water and dried. The crude product was recrystallised from ethanol, m.p. 133-134°C.

65 Ethyl 5-(4-fluoro-2-nitrophenylamino)-2-methylthiazole-4-carboxylate, m.p. 170-174°C, was similarly prepared.

EXAMPLE 3**8-Fluoro-2-methyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b]-[1,5]benzodiazepine**

Ethyl 5-(5-fluoro-2-nitrophenylamino)-2-methylthiazole-4-carboxylate (2.85 g) was hydrogenated at 60 p.s.i. in ethanol (100 ml) with 10% palladium on charcoal (0.35 g). The catalyst was removed and filtration and the solvent removed under reduced pressure to leave the diaminoester which was used without further purification in the next stage.

This diaminoester was stirred in a mixture of N-methylpiperazine (17.65 ml) and anisole (40 ml) under a nitrogen atmosphere. A solution of titanium tetrachloride (2.9 ml) in anisole (15 ml) was added over 5 minutes and the stirred mixture heated at 100°C for 1 hour and then at 160-180°C, under reflux, for 48 hours. After cooling the stirred mixture to about 70°C, a mixture of 20M ammonia solution (5 ml) and 2-propanol (5 ml) was cautiously added. The stirred suspension was allowed to slowly cool to 25°C over 1 hour to precipitate the titanium salts which were then removed by filtration through a pad of celite, washing with ethyl acetate (100 ml). The combined filtrate and washings were extracted twice with 2N hydrochloric acid and the extracts washed with ethyl acetate. The acid solution was basified with 20M ammonia solution and extracted into dichloromethane. After washing with water and drying with magnesium sulphate the solvent was removed under reduced pressure to leave the crude product which was purified by chromatography on a column of magnesium silicate followed by crystallisation from acetonitrile, m.p. 234-237°C.

Similarly prepared were:-

2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b]-[1,5]benzodiazepine, m.p. 258-263°C (acetonitrile)
 7-Fluoro-2-methyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b]-[1,5]benzodiazepine, m.p. 253-255°C (acetonitrile)
 7-Chloro-2-methyl-4-(4-methyl-1-piperazinyl)-10H-thiazolo[5,4-b]-[1,5] benzodiazepine, m.p. 256-264°C (acetonitrile)

EXAMPLE 4

Tablets each containing 10 mg of active ingredient are made up as follows

Active ingredient	10 mg
Starch	160 mg
Microcrystalline cellulose	100 mg
Polyvinylpyrrolidone (as 10% solution in water)	13 mg
Sodium carboxymethyl starch	14 mg
Magnesium stearate	3 mg
Total	300 mg

The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed through a sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

EXAMPLE 5

Capsules each containing 20 mg of medicament are made as follows

Active ingredient	20 mg
Dried starch	178 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, starch and magnesium stearate are passed through a sieve and filled into hard gelatin capsules in 200 mg quantities.

EXAMPLE 6

A freeze dried formulation for reconstitution into an aqueous injection is prepared from the following ingredients

Active ingredient	15 mg
0.1M Hydrochloric acid	0.48 ml
Mannitol	100 mg
Water	to 2 ml

The active ingredient is suspended in water, acidified with hydrochloric acid and mannitol added, and adjusted to pH5. Water is added to 2 ml and the mixture filled into vials and then freeze dried.

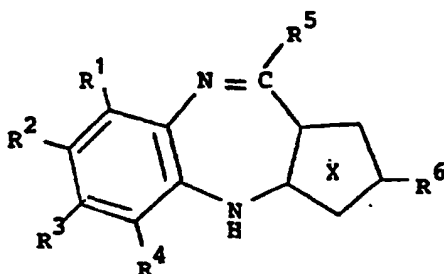
EXAMPLE 7

A sustained release formulation for intra-muscular injection is prepared from the following ingredients

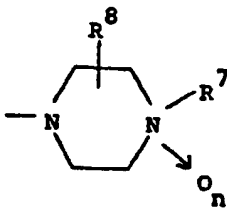
Active ingredient	20 mg
Aluminium stearate	2 mg
Soya bean oil	to 2 ml

Claims

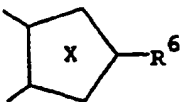
1. A compound of the formula



in which R¹, R², R³ and R⁴ are independently hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, halogen, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkylthio or phenylsulphonyl; in which R⁵ is a group of the formula



where R⁷ is hydrogen or C₁₋₆ alkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl or benzyl or ZO-C₂₋₆ alkyl where Z is hydrogen or an acyl group, R⁸ is hydrogen or C₁₋₄ alkyl and n is 0 or 1, provided that when R⁷ is hydrogen n is 0; in which R⁶ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy or C₁₋₄ alkylthio; and in which

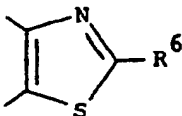


represents a thiazole ring selected from

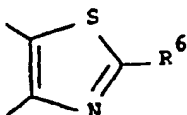


and acid addition salts thereof.

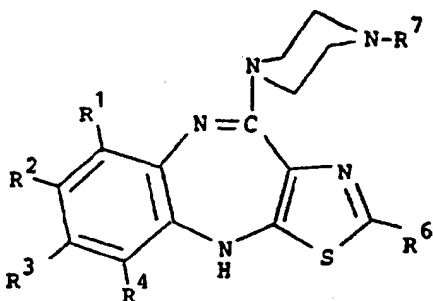
2. A compound according to claim 1 in which the thiazole ring is



3. A compound according to claim 1 in which the thiazole ring is



4. A compound according to claim 2 of the formula



in which R¹, R², R³ and R⁴ independently represent hydrogen, halogen or C₁₋₄ haloalkyl, R⁶ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl or C₁₋₄ alkylthio, R⁷ is hydrogen or C₁₋₄ alkyl.

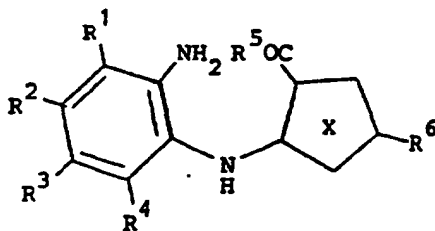
5. A compound according to claim 4 in which R¹ and R⁴ are hydrogen and R² and R³ are independently hydrogen or halogen, R⁶ is C₁₋₄ alkyl and R⁷ is C₁₋₄ alkyl.

6. A compound according to claim 1 for use as a pharmaceutical.

7. A pharmaceutical formulation comprising a compound according to any of claims 1 to 6, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

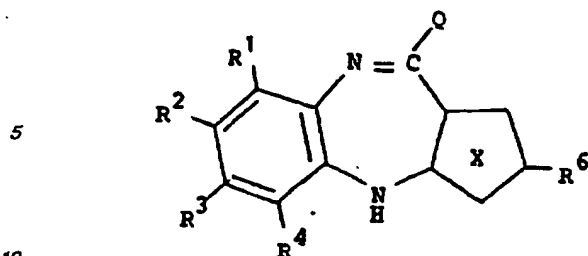
8. A process for producing a compound according to claim 1, which comprises

(a) ring-closing a compound of formula



in which R¹ to R⁶ and X have the values defined in claim 1, optionally followed when R⁷ is hydrogen by alkylation to give a compound in which R⁷ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, benzyl or ZO-C₂₋₆ alkyl where Z is hydrogen or an acyl group,

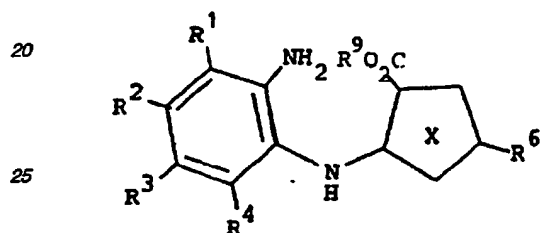
(b) reacting an amine of formula R⁵H with a compound of formula



in which R¹ to R⁶ and X have the values defined in claim 1 and Q represents a radical capable of being split off with the hydrogen atom of the amine R⁵H, optionally followed when R⁷ is hydrogen by alkylation to give a compound in which R⁷ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, benzyl or ZO-C₂₋₆ alkyl where Z is hydrogen or an acyl group, or

(c) oxidising a compound according to claim 1, in which R⁷ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, benzyl or ZO-C₂₋₆ alkyl where Z is an acyl group and n is 0, to give a compound in which n is 1.

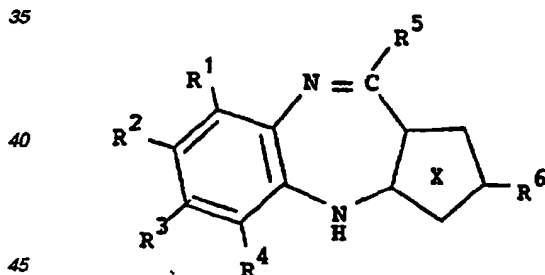
9. An intermediate compound of the formula



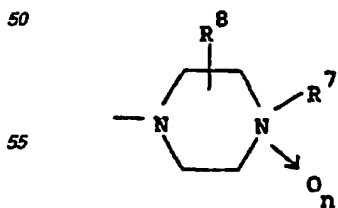
in which R¹, R², R³, R⁴, R⁶ and X are as defined in claim 1, and R⁹ is an ester group.

Claims for the following Contracting States: ES + GR

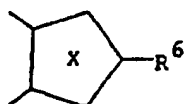
1. A process for producing a compound of the formula



in which R¹, R², R³ and R⁴ are independently hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, halogen, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkylthio or phenylsulphonyl; in which R⁵ is a group of the formula



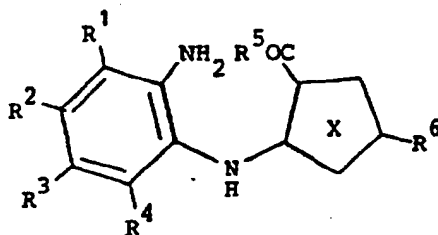
where R⁷ is hydrogen or C₁₋₆ alkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl or benzyl or ZO-C₂₋₆ alkyl where Z is hydrogen or an acyl group, R⁸ is hydrogen or C₁₋₄ alkyl and n is 0 or 1, provided that when R⁷ is hydrogen n is 0; in which R⁶ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy or C₁₋₄ alkylthio; and in which



represents a thiazole ring selected from

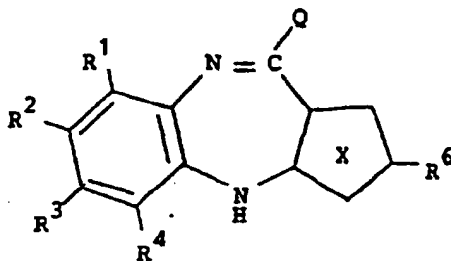


and acid addition salts thereof; which comprises
(a) ring-closing a compound of formula



in which R^1 to R^6 and X have the values defined above, optionally followed when R^7 is hydrogen by alkylation to give a compound in which R^7 is C_{1-6} alkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, benzyl or $ZO-C_{2-6}$ alkyl where Z is hydrogen or an acyl group,

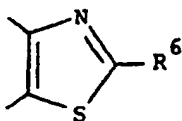
(b) reacting an amine of formula R^5H with a compound of formula



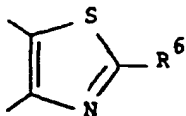
in which R^1 to R^6 and X have the values defined above and Q represents a radical capable of being split off with the hydrogen atom of the amine R^5H , optionally followed when R^7 is hydrogen by alkylation to give a compound in which R^7 is C_{1-6} alkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, benzyl or $ZO-C_{2-6}$ alkyl where Z is hydrogen or an acyl group, or

(c) oxidising a compound according to claim 1, in which R^7 is C_{1-6} alkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, benzyl or $ZO-C_{2-6}$ alkyl where Z is an acyl group and n is 0, to give a compound in which n is 1.

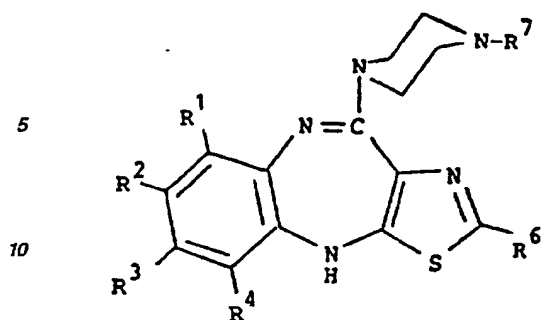
2. A process for producing a compound according to claim 1 in which the thiazole ring is



3. A process for producing a compound according to claim 1 in which the thiazole ring is



4. A process for producing a compound according to claim 2 of the formula



in which R¹, R², R³ and R⁴ independently represent hydrogen, halogen or C₁₋₄ haloalkyl, R⁶ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₄ alkyl or C₁₋₄ alkylthio, R⁷ is hydrogen or C₁₋₄ alkyl.

5. A process for producing a compound according to claim 4 in which R¹ and R⁴ are hydrogen and R² and R³ are independently hydrogen or halogen, R⁶ is C₁₋₄ alkyl and R⁷ is C₁₋₄ alkyl.

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(51) Int. Cl.⁵: **C07D 513/04, C07D 277/56, A61K 31/425, //(C07D513/04, 277:00,243:00)**

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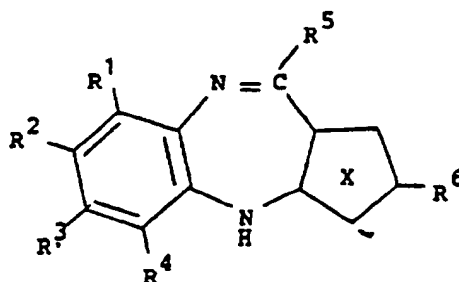
(88) Date of deferred publication of the search report:
03.04.91 Bulletin 91/14

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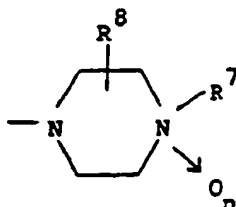
(71) Applicant: **LILLY INDUSTRIES LIMITED**
Kingsclere Road

(54) **Benzodiazepine compounds and their use as pharmaceuticals.**

(57) **Pharmaceutical thiazolo-[1,5]benzodiazepines of the formula**



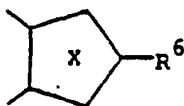
in which R¹, R², R³ and R⁴ are independently hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, halogen, C₁₋₄ haloalkyl, nitro, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, C₁₋₄ alkylthio or phenylsulphonyl; in which R⁵ is a group of the formula



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where R^7 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, benzyl or $ZO-C_{2-6}$ alkyl where Z is hydrogen or an acyl group, R^8 is hydrogen or C_{1-4} alkyl and n is 0 or 1, provided that when R^7 is hydrogen n is 0; in which R^6 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or C_{1-4} alkylthio; and in which



represents a thiazole ring selected from



and acid addition salts thereof.

The compounds have central nervous system activity.



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EUROPEAN SEARCH REPORT

Application Number

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Page 1

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A, D	GB-A-1533235 (LILLY INDUSTRIES LTD.) * page 3, lines 1 - 4 * * page 6, lines 18 - 33 * * page 8, lines 1 - 14 * * claims 19, 20, 25, 37, 41 * ---	1, 4, 6-9	C07D513/04 C07D277/56 A61K31/425 //(C07D513/04, 277:00,243:00)
A	CHEMICAL ABSTRACTS, vol. 93, no. 17, 27 October 1980 Columbus, Ohio, USA J. K. CHAKRABARTI et al.: "Heteroarenebenzodiazepines. 3, 4-Piperazinyl-10 H-thieno[2,3-b][1,5]benzodiazepines as potential neuroleptics" page 21; ref. no. 160947N & J. Med. Chem. 1980, 23[8], 878-84 * abstract *	1, 4, 6	
A	US-A-3897446 (J.B. HESTER, JR.) * abstract; claim 1 *	1, 6	
A	CHEMICAL ABSTRACTS, vol. 98, no. 11, 14 March 1983 Columbus, Ohio, USA M. SUZUKI et al.: "Synthesis of amino acids and related compounds. Part 25. A new convenient synthesis of 5-amino-1,3-thiazole-4-carboxylic acids" page 546; ref. no. 892282 & Synthesis, no. 10, 1982, pages 874-875 * abstract *	9	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07D277/00 C07D513/00
A	CHEMICAL ABSTRACTS, vol. 102, no. 21, 27 May 1985 Columbus, Ohio, USA E. K. MIKITENKO et al.: "Reaction of 4-amino-2-methylthio-5-phenylthiazole with acetoacetic ester" page 573; ref. no. 185000R & Ukr. Khim. Zh. [Russ. Ed.] 1984, 50[11], 1203-5 * abstract *	9	
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 22 JANUARY 1991	Examiner HASS C.
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X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document I : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application F : document cited for other reasons * : member of the same patent family, corresponding document			

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A, D	ARCHIV DER PHARMAZIE UND BERICHTE DER DEUTSCHEN PHARMAZEUT. GESELLSCHAFT, vol. 303, no. 8, 1970, Weinheim, DE, pages 625 - 633; K. HARTKE et al.; "N-Cyan-thiolidoester und N,N'-Dicyan-amidine" * page 630, formula 12 *		
A, D	LIEBIGS ANNALEN DER CHEMIE, no. 4, 1986, Weinheim, DE, pages 780 - 784; W. RIED et al.; "Thiazolsynthesen mit N-Cyanimidsäureestern oder 3-Cyanisoharnstoff und Thioglycolsäurederivaten" * page 780, compounds 3a-g, 4a-d *		
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 22 JANUARY 1991	Examiner HASS C.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background D : non-written disclosure P : intermediate document T : theory or principle underlying the invention F : earlier patent document, but published on, or after the filing date I : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document			

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